CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-535

ADMINISTRATIVE DOCUMENTS

PATENT AND EXCLUSIVITY INFORMATION (ITEM 13)

1. **Active Ingredient:** Clobetasol propionate (USAN)

2. **Strength:** 0.05% (0.5 mg/g)

3. **Trade Name:** CLOBEX™ LOTION

4. **Dosage Form and Route of Administration:** Lotion, Topical application to the skin

5. **Applicant Firm Name:** GALDERMA Laboratories, L.P.

   The applicant, GALDERMA Laboratories, L.P., is a coorporate entity doing business in the United States at 14501 North Freeway, Fort Worth, Texas 76177.

6.

Applicant Patent	Expiration Date	Patent Holder
6,106,848	September 22, 2017	Centre International de Recherche Dermatologiques (C.I.R.D.) Valbonne, FRANCE

U.S. Agent for the Patent Holder

Norman Stepno, Esq
Burns, Doane, Swecker & Mathis, L.L.P.
699 Prince St.
Alexandria, VA 22314

7. Brief Description of Each Patent which Claims the Drug

Patent No.

6,106,848 claims a stable, topically applicable oil-in-water bioaffecting emulsions having intermediate viscosity, characteristically ranging from 3 to 10 Pa•s, comprise (a) from 30% to 50% by weight of at least one pro-penetrating glycol, (b) at least one emulsifying agent, advantageously an anionic ampliphilic polymer, and (c) at least one biologically active agent, for example an active agent that modulates skin differentiation and/or proliferation and/or pigmentation, an anti-inflammatory, and antibacterial, an antifungal, etc.

8. Claimed Exclusivity (21 CFR 314.50 (j))

1. The applicant, GALDERMA Laboratories, L.P., claims 3 years marketing exclusivity upon approval of the drug product that is the subject of this New Drug Application submitted pursuant to section 505(b) of the FD&C Act.

2. The applicant makes reference to 21 CFR 314.108 (b)(4) in support of this claim.

Claimed Exclusivity - 21 CFR 314.50 (j)

i. *New clinical investigation*: The applicant certifies that to the best of its knowledge the Phase III safety and efficacy clinical investigation included in the application meets the definition of "new clinical investigation" set forth in 314.108 (a).

ii. *Essential to approval*: The applicant certifies that it has thoroughly searched in the scientific literature and, to the best of the applicant's knowledge, there are no known publications wherin a lotion dosage form of Clobetasol propionate in any strength has been studied for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Furthermore, there are no published studies or publicly available reports to provide sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation in this application submitted pursuant to section 505 (b)(2) of the FD&C Act.

iii. *Conducted or sponsored by*: The applicant certifies that it was the sponsor named in the Form FDA 1571 for Investigational New Drug Application (IND) — under which the new clinical investigation that is essential to the approval of this application was conducted.

25 Sept 02

Date

Paul Clark

Signature

Paul CLARK
Vice President
Regulatory Affairs
GALDERMA Laboratories, L.P.

EXCLUSIVITY SUMMARY for NDA # 21-535 SUPPL #

Trade Name Clobex Generic Name clobetasol propionate

Applicant Name Galderma Laboratories, L.P. HFD-540

Approval Date July 24, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      N/A

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      N/A

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-340	Temovate E Emollient Cream
NDA # 19-322	Temovate E Cream
NDA # 21-142	Olux Foam
NDA # 19-322	Temovate Ointment
NDA # 19-966	Temovate Solution
NDA # 20-337	Temovate Gel

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could

independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 9707 U.S. pivotal

Investigation #2, Study # 18001 U.S. pivotal

Investigation #3, Study # 2651 Supportive European

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /__X_/
Investigation #3	YES /___/	NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study #9701

Investigation #_2_, Study # 18001

Investigation #_3_, Study # _2651

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 54,230 YES /_X_/ NO /___/ Explain:

Investigation #2

IND # 54,230 YES /_X_/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____ July 24, 2003
Melinda Harris, M.S. Date
Project Manager

_____ July 24, 2003
Jonathan Wilkin, M.D. Date
Division Director

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Melinda Harris
7/24/03 03:05:11 PM

Jonathan Wilkin
7/24/03 03:13:11 PM

DEBARMENT CERTIFICATION
(ITEM 16)

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and pursuant the Draft Guidance "Submitting Debarment Certification Statements" dated September 1998, the applicant (GALDERMA Laboratories, L.P) makes the following statement in connection with this New Drug Application for Clobetasol Propionate Lotion, 0.05%.

GALDERMA Laboratories, L.P hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

25-Sept 02
Date

Paul Clark
Signature

Paul CLARK
Vice President
Regulatory Affairs
GALDERMA Laboratories, L.P.

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-535 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: 9/27/02 Action Date: 7/27/03

HFD-540 Trade and generic names/dosage form: Clobex (clobetasol propionate lotion), 0.05%

Applicant: Galderma Laboratories, L.P. Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of steroid responsive dermatoses

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ___Partial Waiver ___Deferred __X__Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval

- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.** 0	**yr.** 12	**Tanner Stage**_____
Max_____	**kg**_____	**mo.** 11	**yr.** 17	**Tanner Stage**_____

Comments:

This drug is not recommended in the pediatric age group because of the high rate of HPA axis suppression found in the adolescent safety study.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Melinda Harris, M.S.
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze

(revised 9-24-02)

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Melinda Harris
7/22/03 03:27:28 PM

Denise Cook
7/22/03 03:31:33 PM

Jonathan Wilkin
7/22/03 05:23:02 PM

Division Director's Summary Review of NDA 21-535

Sponsor:	Galderma Laboratories, L.P. 14501 North Freeway Forth Worth, TX 76177 USA
Generic name:	Clobetasol Propionate
Trade name:	Clobex
Chemical name:	Clobetasol Propionate
Pharmacologic Category:	Anti-inflammatory
Indication:	Moderate to Severe Plaque Psoriasis and — Dermatitis
Dosage Forms (s):	Lotion
Route (s) of Administration:	Topical

I. Reviewing Disciplines' Conclusions:

A. Chemistry Review dated 6/27/03:

"After evaluation for GMP compliance, all three manufacturing and testing facilities were found to be acceptable. Clobetasol propionate, is a well-established chemical whose structure has been fully elucidated. It is characterized through the USP monograph, and listed in USAN and in the Merck Index (additional data). The DMF of the main drug substance supplier has been updated, reviewed and found to be adequate. The NDA submission and its amendments (responses to information request letters) provide adequate information on the chemistry, manufacturing and controls for the production of Clobex (clobetasol propionate) Lotion, 0.05%.

"From a chemistry, manufacturing and controls standpoint (sic: it) is approvable pending action by the applicant to withdraw [redacted] as an alternate [redacted] supplier."

The applicant withdrew the reference to DMF [redacted] pertaining to [redacted] in correspondence dated July 1, 2003, resolving the sole remaining CMC approvability issue.

B. Pharmacology/Toxicology Review dated 3/20/03:

"The nonclinical studies conducted by the sponsor confirm that clobetasol propionate has teratogenic potential. A teratogencity study in rats using the dermal route resulted in dose related maternal toxicity and fetal effects from 0.05 to 0.5 mg/kg/day of Clobetasol propionate. These doses are approximately 0.14 to 1.4 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included low fetal weights, umbilical herniation, cleft palate, reduced skeletal ossification other skeletal abnormalities. Other nonclinical findings suggest that the lotion did not cause skin sensitization and was not irritating to the skin or eye."

No new pharmacology information was submitted by the sponsor, since this was a 505(b)(2).

"No new safety issues relevant to clinical use have been identified in the studies conducted by the sponsor. The teratogenic potential of clobetasol propionate is addressed in the label.

"The application is approvable from a pharm/tox perspective provided the sponsor agrees to conduct the recommended phase 4 nonclinical studies.

"It is recommended that the sponsor be asked to agree to conduct a dermal carcinogenicity study and an evaluation of the photocarcinogenic potential of the drug product as phase 4 commitments."

C. Clinical Pharmacology & Biopharmaceutics Review dated 7/1/03:

"From a Biopharmaceutics perspective the firm has provided evidence of systemic availability for the test Clobex Propionate Lotion and reference Temovate E Emollient cream formulations. Based on the results of the 3 HPA axis trials, use of CP Lotion is clearly associated with a high incidence of HPA suppression compared to the Temovate E Emollient cream. Thus, from a clinical pharmacology perspective, there is a reasonable concern about the safety of this product in uncontrolled administration. While the bioavailability of clobetasol has been determined via indirect methods (i.e., HPA axis testing), the safety issues raised by the increased bioavailability relative to the reference product raises a significant concern."

The basis for the "significant concern" is that this product is "clearly associated with a high incidence of HPA suppression compared to the Temovate E Emollient Cream." This "significant concern" of "the safety issues raised by the increased bioavailability" will be addressed in the discussion of the Clinical Review (below).

D. Biostatistics Review dated 5/7/03:

The ITT analysis with LOCF for missing data demonstrated that Clobex Lotion is superior to its vehicle for all primary endpoints in Studies 9707 (psoriasis), 18001 (atopic dermatitis), and 2651 (psoriasis). Study 2651 was regarded as supportive and Studies 9707, and 18001 as pivotal, by both the Biostatistics and Clinical disciplines.

Formal statistics for the HPA axis suppression studies were not described in the Biostatistics Review, and the small numbers of subjects tested for HPA axis suppression do not readily invite formal statistical analysis.

"From statistical point of view, the safety profile of Clobex Lotion is comparable to those Temovate E Cream (or Dermoval Cream for Study 2651) and Lotion vehicle in terms of the incidence of adverse events and cutaneous skin reaction."

The essential findings in the Biostatistics Review are the same as found in the Clinical Review, where they will be discussed (below) in the regulatory context of a 505(b)(2) submission.

E. Clinical Review dated (by Team Leader) 06/12/03:
The Medical Officer and Team Leader describe multiple conclusions:

1. "There is no doubt that clobetasol propionate as chemical moiety in a topical formulation is a super high potency anti-inflammatory drug product capable of treating corticosteroid responsive dermatoses. This was demonstrated in the two pivotal trials. Clobetasol propionate lotion (CP Lotion) was statistically superior to its lotion vehicle ($p \leq 0.001$)."
2. "In terms of efficacy, the Division allows for a 10% margin of non-inferiority compared to the RLD. In both the psoriasis trial and the atopic dermatitis trial, clobetasol propionate lotion had a margin of greater than 10% inferiority as compared to Temovate E (18.9% and 12.0%, respectively). In the atopic dermatitis trial, where the margin was closer to 10%, CP lotion failed in 3 of the 4 secondary variables, erythema, oozing/crusting, and pruritus."
3. "In terms of safety, while the cutaneous safety profiles of the two drug products are similar, the systemic safety profile, which in my opinion, is the major issue, of clobetasol propionate lotion is much worse than that of Temovate E Emollient Cream. The endpoint examined for systemic safety was the potential to suppress the HPA axis. CP Lotion

— However, this drug caused HPA axis suppression at some point during treatment of psoriasis in 80% of patients as compared to 33% in patients treated with Temovate E. Furthermore, at the end of the study 40% of patients had HPA axis suppression compared to 0% treated with Temovate E. This study further demonstrates that the potential for HPA axis suppression by clobetasol propionate lotion may be underestimated as the adrenal glands of the patients were constantly being stimulated (almost q week during the study) and suppression still occurred at the endpoint (4 weeks) for patients on CP Lotion but not in patients on Temovate E. Lastly, although the BSA treated in this study was higher than that approved for Temovate E, one has to assume that the comparison of the proportion of suppression between the two drugs, although lower, would be the same."
4. "The greater ability of CP lotion to cause HPA axis suppression is substantiated in the atopic dermatitis studies, of which the adolescent study is demonstrative. In this study 64.3% of patients experienced HPA axis suppression on CP lotion compared to 20% of those who used Temovate E."
5. "The time to recovery from HPA axis suppression was not clear for all the patients who had follow-up. A greater number did not recover in the time tested who were treated with clobetasol propionate lotion as compared to Temovate E Emollient Cream."
6. "The question to be answered ultimately in review of this application, when considering the risk/benefit analysis of clobetasol propionate lotion, is, ' Does clobetasol propionate lotion offer any advantage in the interest of the public health over the clobetasol propionate formulation that is currently marketed?' In my opinion, the answer is, 'No, it does not offer any advantage.' It is not efficacious as Temovate E Emollient Cream in treating corticosteroid responsive dermatoses while at the same time presents an

increased risk to the safety of the public health by having a poorer systemic safety profile as compared to Temovate E Emollient Cream."

The Medical Officer and Team Leader recommend "that the action taken for the new drug application of clobetasol propionate lotion be that of non-approvable."

I agree with some of their conclusions and not with others:

1. I agree that Clobex Lotion is superior to its lotion vehicle in effectiveness.
2. I agree that there was insufficient evidence to conclude that Clobex Lotion is non-inferior to the reference listed drug product, Temovate E Emollient Cream; however, I disagree that this would be an essential requirement for approval (see below).
3. I agree that the local safety profile is similar for Clobex Lotion and Temovate E Emollient Cream.
4. I disagree that the systemic safety profile of Clobex Lotion (which is regarded as " the major issue" in the Clinical Review) is "much worse than that of Temovate E Emollient Cream" (see below).
5. I agree that 9 of 14 adolescent patients with atopic dermatitis had evidence of HPA axis suppression associated with Clobex Lotion. This product will be indicated for adults only.
6. I disagree that "the question to be answered ultimately in review of this application, when considering the risk/benefit analysis of clobestasol propionate lotion, is, 'Does clobetasol propionate lotion offer any advantage in the interest of the public health over the clobetasol propionate formulation that is currently marketed'?" Pages 27-29 of Reinventing Drug & Medical Device Regulations, National Performance Review (April 1995) address the " Effectiveness of Drugs and Devices." The key passage states: " For the majority of new drugs and Class III devices, i.e., new products intended to treat less serious illness or provide relief from symptoms, a showing of effectiveness is usually based on a clinical trial comparing the product to a placebo. Such a showing does not involve a comparison to any other product."

I will address the remaining disagreements, which are 1) whether there is a requirement for demonstrating non-inferiority (in efficacy) to the reference listed drug product and 2) whether the systemic safety (HPA axis suppression) profile of Clobex Lotion is "much worse" than that of the reference listed drug product in the following analysis of this NDA.

The essential feature of a 505 (b)(2) application is that the applicant may rely on the Agency's finding of efficacy and/or safety from the labeling of a reference listed drug product by sufficiently comparing the bioavailabilities of their test product with the reference listed drug product. For topical products, bioavailability comparisons are generally obtained from clinical trials employing the endpoints of efficacy and safety. For topical corticosteroids there is generally also a comparative HPA axis suppression test (or tests, in the case of different dosing regimens in the same application).

The analysis of a 505 (b)(2) approach begins with the determination of the informational needs for a 505(b)(1) application according to current standards. Often, the reference listed drug product does not have labeling information sufficient for current standards, and the applicant must supply such additional information through studies they have conducted or obtained by right of reference. Also, the applicant may provide adequate information demonstrating efficacy or some aspect of safety that meets the needs for a 505(b)(1) application, such that they need not rely on the Agency's finding

from the labeling of the reference listed product for that particular informational need. Thus, the comparison of bioavailabilities with the reference listed drug product needs only to support the Agency's finding from the labeling of a reference listed drug product of that specific, essential information piece not otherwise provided by the applicant's studies or through right of reference.

Often, topical product NDAs are 505 (b)(2) applications in which the sponsor relies on the Agency's finding of efficacy from the labeling of a reference listed drug product, e.g., when the vehicle is sufficiently different from that of the reference listed drug product owned by a different manufacturer. In such cases, the sponsor must demonstrate non-inferiority to the reference listed drug product and superiority to the new vehicle. Although this has been a common architectural feature of the information structure in many 505 (b)(2) applications, the finding of non-inferiority to the reference listed drug product is not essential, if the applicant provides sufficient information separately to document effectiveness. The comparative bioavailability bridge need only support the Agency's finding from the labeling of the reference listed drug product for which the applicant has not otherwise produced sufficient evidence through studies they have conducted or through right of reference.

This NDA adduces sufficient evidence for efficacy for a 505 (b)(1) application, viz., two adequate and well-controlled studies (9707 and 18001) in which the product is clearly superior to vehicle. Accordingly, there is no need to demonstrate non-inferiority to the referenced listed drug product, since the applicant is not relying on the Agency's finding of efficacy from the labeling of the reference listed drug product. The demonstration of superiority to vehicle in psoriasis and atopic dermatitis in separate studies is sufficient for the corticosteroid – responsive dermatoses indication.

In addition to evidence for efficacy, the analysis of a 505 (b)(2) approach involves the determination of the informational needs for safety for a 505(b)(1) application according to current standards. Evidence for safety is divided into two parts: non-clinical and clinical. The first part, non-clinical, has not been established independently by the applicant in this NDA, and the applicant is relying on the Agency's finding of non-clinical safety from the labeling of the reference listed drug product. Also, the applicant has made specific post-marketing commitments to provide additional non-clinical safety information for informational needs that could be provided post-approval for the same product in a strictly 505 (b)(1) application.

The clinical evidence for safety in this NDA is divided into two parts: local and systemic. Both the Clinical Review and the Biostatistics Review conclude that Clobex Lotion and Temovate E Emollient Cream have similar local safety findings. Both the Clinical Review and the Biostatistics Review conclude that Clobex Lotion was not found to be non-inferior to Temovate E Emollient Cream according to the efficacy endpoints. Accordingly, the logic of 320.24 (b)(4) would indicate that the rate and extent of absorption of the active ingredient in Clobex Lotion at the site of action, viz., locally, would be at most equivalent to, and plausibly somewhat less than, Temovate E Emollient Cream. If Clobex Lotion is at most equivalent to Temovate E Emollient Cream, then it is permissible to rely on the Agency's findings of local safety for the active moiety from the labeling of the reference listed drug product. The additional evidence for local safety from studies 9707, 2651, and 18001 and from the requisite human dermal safety studies,

2129 and 1802, is sufficient to conclude that the local safety information base is adequate and that local safety is acceptable for the intended use of the product.

The clinical evidence for systemic safety for topical (gluco-) corticosteroids is generally derived from HPA axis suppression studies. There are general aspects of such HPA axis suppression studies and utility of outcomes that are independent of this specific NDA that must be considered before addressing the evidence in this NDA. Importantly, the primary clinical utility of HPA axis suppression study outcomes is whether HPA axis may occur at maximal duration, amount per week, and body surface area involved, according to labeled conditions of use. Very precise point estimates of HPA axis suppression "risk" provide minimal additional utility, since there are many variables that determine whether suppression occurs, such as prior corticosteroid use, body surface area of involvement, anatomic region of involved skin, thickness of product application, etc. It is not uncommon for HPA axis suppression studies to show suppression in patients with smaller body surface areas of involvement compared with patients with larger body surface areas of involvement who do not suppress. There is no adequate model based on these variables that can predict who will suppress. Accordingly, it is not possible to incorporate a very precise point estimate from HPA axis suppression studies of new drug products into a heuristic that will allow a clinician to determine which patient is at risk for suppression. At best, HPA axis suppression studies can identify risk at maximal conditions of labeled use as unlikely, possible, or probable.

Because of the multiple degrees of freedom in the topical corticosteroid-induced adrenal suppression model, the ability of comparative adrenal suppression studies to detect true differences in the potential for adrenal suppression between two products depends on the numbers of subjects tested and the degree to which the identifiable variables are controlled. In most comparative adrenal suppression studies the large number of identifiable variables and difficulty in recruiting such patients into the study preclude strong inferences regarding differences in potential for adrenal suppression between two products, especially when numbers of subjects actually tested are small.

This NDA includes studies of HPA axis suppression comparing Clobex Lotion and Temovate E Emollient Cream for both four weeks' duration in adult patients with psoriasis (Study 9708) and two weeks' duration in adult patients with atopic dermatitis (Study 18009). In Study 9708, 8 of 10 patients suppressed with Clobex Lotion and 3 of 10 patients suppressed with Temovate E Emollient Cream. The requisite condition for the Chi-Square Test, a minimum of 5 per cell, is not met, since half of the cells have counts less than 5. Two-sided Fisher's Exact Test computationally gives $p \leq 0.07$; however, for this test the assumption of fixed margins is very restrictive for interpretation of findings. Simply stated, the denominators are too small to provide strong inferences by statistical methods. In Study 18009, 5 of 9 patients suppressed with Clobetasol Lotion and 4 of 9 patients suppressed with Temovate E Emollient Cream. Two-sided Fisher's Exact Test computationally gives a probability of 1.00; however, for this test the assumption of fixed margins is very restrictive for interpretation of findings. The denominators are even smaller than Study 18009. Thus, in adult patients with psoriasis and atopic dermatitis, Clobex Lotion demonstrated rates of HPA axis suppression that were numerically higher than those of Temovate E Emollient Cream, although the small numbers studied do not allow for strong statistical inferences that Clobex Lotion is

"much worse" than Temovate E Emollient Cream in the potential for causing HPA axis suppression.

However, it is fair to state that both Clobex Lotion and Temovate E Emollient Cream present a relatively high risk for HPA axis suppression when used at maximal conditions of labeled use. There are clear statements of such risk in the final draft labeling agreed to by the sponsor, along with limiting the indication to adults only and stating explicitly that "use in patients younger than 18 years of age is not recommended due to numerically high rates of HPA axis suppression."

In sum, I find that adequate evidence has been provided in this NDA to find that this product is safe and effective for its intended use per labeled conditions, including precautionary language regarding the potential for HPA axis suppression. A post-marketing commitment to conduct HPA axis suppression tests without interim adrenal stimulation will provide useful information for product labeling in the future

F. Conclusion

This NDA is sufficient for approval since the sponsor has committed to perform the recommended post-marketing studies, both non-clinical and clinical, and has accepted the final draft labeling proposed to sponsor.

/S/

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
7/24/03 03:03:14 PM
MEDICAL OFFICER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 11/19/02	DUE DATE: 6/6/03	ODS CONSULT #: 02-0213

TO:

Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH:

Melinda Harris, M.S.
Project Manager, Division of Dermatologic and Dental Drug Products
HFD-540

PRODUCT NAME:	**NDA SPONSOR:** Galderma Laboratories, L.P.
Clobex (Clobetasol Propionate Lotion) 0.05% NDA #: 21-535	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products (HFD-540), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Clobex" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name, "Clobex". This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
2. DDMAC finds the proprietary name, "Clobex", acceptable from a promotional perspective.
3. Provide final labels and labeling once available for review and comment.
4. We recommend consulting Dan Boring (of the USAN council and LNC) for the proper designation of the established name.

/S/

Carol Holquist, R.Ph.
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Division of Medication Errors and Technical Support
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/S/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 25, 2003

NDA NUMBER: 21-535

NAME OF DRUG: Clobex (Clobetasol Propionate Lotion) 0.05%

NDA HOLDER: Galderma Laboratories, L.P.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) for assessment of the tradename "Clobex", regarding potential name confusion with other proprietary and established drug names. DMETS also reviewed and commented on submitted draft labels and labeling.

PRODUCT INFORMATION

"Clobex" is the proposed proprietary name for clobetasol propionate lotion, 0.05%, which is a synthetic fluorinated corticosteroid for topical dermatologic use. Clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. It is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses as wells as for the treatment of moderate to severe plaque-type psoriasis. "Clobex" should be applied to the affected skin areas twice daily and rubbed in gently and completely. For inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, application should be limited to two consecutive weeks while for moderate to severe plaque-type psoriasis, treatment should be limited to four consecutive weeks. The total dosage should not exceed 50 g [redacted] per week. This drug product will be supplied in 1 fl.oz [redacted], 2 fl.oz [redacted], and 4 fl.oz. [redacted] bottles.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

look alike to "Clobex" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[5] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Clobex". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Panel had look-alike and sound-alike concerns with *Cobex-Vitamin B12,* and *Rubex* as well as sound-alike concerns with *Klotrix* and *Probax*. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

2. DDMAC did not have concerns about the name "Clobex" with regard to promotional claims.

3. DMETS also had sound-alike concerns with *Clorpres* and *Klorvess*. These products are also listed in Table 1 (see page 4).

Table 1

Product Name	Dosage form(s), Generic name	Usual adult dose	Other**
Clobex	Clobetasol Propionate (Rx) Lotion: 0.05%	Apply to affected skin areas twice daily	
Cobex	Vitamin B12 (Year of Last Recorded Sales: 1991)	N/A	SA/LA
Rubex	Doxorubicin (Rx) Powder for Injection: 50 mg	60 to 75 mg/m^2 as a single IV injection administered at 21-day intervals.	SA/LA
Klotrix	Potassium Chloride (Rx) Tablet (controlled-release): 10 mEq	Hypokalemia Prevention 16 to 24 mEq/day. Potassium Depletion 40 to 100 mEq or more per day.	SA
Probax	Propolis, Petrolatum, Mineral Oil, and Lanolin	N/A	SA

[4] WWW location http://www.uspto.gov.

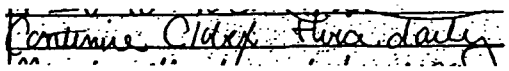
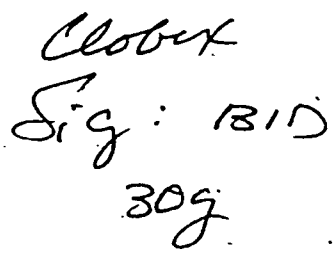
[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Product Name	Dosage form(s); Generic name	Usual adult dose	Other**
Clobex	Clobetasol Propionate (Rx) Lotion 0.05%	Apply to affected skin areas twice daily.	
	(OTC: Year of last recorded sale - 2000) Gel: 2% propolis		
Clorpres	Clonidine Hydrochloride and Chlorthalidone (Rx) Tablet: 0.1 mg/ 15 mg; 0.2 mg/15 mg, and 0.3 mg/15 mg	One tablet once or twice a day (maximum per day: 0.6 mg/30 mg).	SA
Klorvess	Potassium Chloride (Rx) Tablet, effervescent: 20 mEq	Hypokalemia Prevention 16 to 24 mEq/day. Potassium Depletion 40 to 100 mEq or more per day.	SA
*Frequently used, not all-inclusive. **SA (sound-alike), LA (look-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

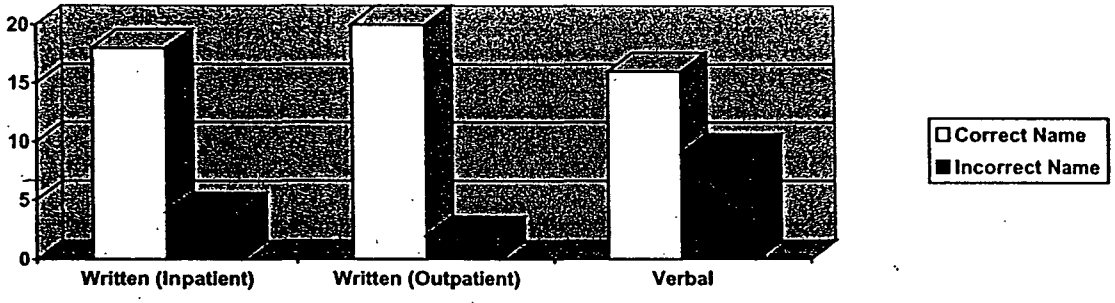
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Clobex" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Clobex" (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient Rx: 	*Outpatient Rx:* Clobex. Twice a day. 30 grams.
Outpatient Rx: 	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Clobex"	Incorrectly Interpreted
Written Inpatient	35	22 (63%)	18 (82%)	4 (18%)
Written Outpatient	32	22 (69%)	20 (91%)	2 (9%)
Verbal Outpatient	39	25 (64%)	16 (64%)	9 (36%)
Total	106	69 (65%)	54 (78%)	15 (22%)



Among the inpatient written prescriptions, 4 (18%) out of 22 respondents interpreted "Clobex" incorrectly. Incorrect interpretations included *Clabex* (4 respondents, 18%). None of the respondents misinterpreted "Clobex" as an existing U.S. marketed drug product.

Among the outpatient written prescriptions, 2 (9%) out of 22 respondents interpreted "Clobex" incorrectly. Incorrect interpretations included *Clobes* (1 respondent, 5%) and *Clebex* (1 respondent, 5%). None of the respondents misinterpreted "Clobex" as an existing U.S. marketed drug product.

Among the outpatient verbal prescriptions, 9 (36%) out of 25 respondents interpreted "Clobex" incorrectly. Incorrect interpretations included *Clobax* (4 respondents, 16%), *Clovex* (3 respondents, 12%), *Clovax* (1 respondent, 4%), and *Chlorba* (1 respondent, 4%). None of the respondents misinterpreted "Clobex" as an existing U.S. marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Clobex", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The proprietary names that were of concern are *Rubex, Klotrix, Clorpres,* and *Klorvess.* It appears from the IMS data obtained from Thomson & Thomson that *Cobex* and *Probax* [redacted] Therefore, analysis of the potential risk of confusion between *Cobex* and "Clobex" as well as *Probex* and "Clobex" was not conducted.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that "Clobex" can be confused with existing drugs on the U.S. market. All of the interpretations from the verbal and written prescription studies were phonetic/misspelled variations of the drug name "Clobex". However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

Rubex sounds and looks similar to "Clobex". *Rubex* contains doxorubicin and is indicated to produce regression in disseminated neoplastic conditions. Both names may sound similar due to the overlap in the "bex" sound. However, the pronunciation of the "ru" in *Rubex* is distinguishable from "clo" in "Clobex". Also when scripted, *Rubex* can be differentiated from "Clobex" due to the differences in the scripting of "Ru" and "Clo", respectively, even though both names contain the "bex" ending. Even though these drug products are only available in one strength and overlap in strength numbers, they do differ in strength (50 mg vs. 0.05%) and the expression of strength. They also differ in dosage form (powder for injection vs. lotion), route of administration (parenteral vs. topical), and different directions of use (60 to 75 mg/m^2 IV injection administered at 21-day intervals vs. apply to affected skin areas twice daily). These differences and the context of use would decrease the potential risk of a medication error occurring between these two drug products.

Klotrix sounds similar to "Clobex". *Klotrix* contains potassium chloride and is indicated for the treatment of hypokalemia in various conditions as well as prevention of potassium depletion when dietary intake is inadequate in various conditions. *Klotrix* sounds similar to "Clobex" since "Klo" in *Klotrix* is pronounced the same as "Clo" in "Clobex". Even though the pronunciation of "ix" in *Klotrix* is similar to "ex" in "Clobex", the sound of the "trix" in *Klotrix* may sound different than "bex" in "Clobex". Even though both drug products are only available in one strength (10 mEq vs. 0.05%) and can be administered twice a day, they differ in dosage form (lotion vs. tablet) and route of administration (topical vs. oral). These differences would decrease the potential risk of a medication error occurring between these two drug products. Also, according to the data provided by Thomson and Thomson, [redacted], which would decrease the potential risk of a medication error even further.

Clorpres sounds similar to "Clobex". *Clorpres* is a combination product that contains clonidine hydrochloride and chlorthalidone and is indicated for the treatment of hypertension. *Clorpres* sounds similar to "Clobex" since both names begin with the sound "Clo". The "pres" and "bex" ending also sounds similar. Both products can be given twice a day and overlap in prescriber and patient population. However, *Clorpress* and "Clobex" differ in strengths (0.1 mg/15 mg, 0.2 mg/15 mg, and 0.3 mg/15 mg vs. 0.05%) where there is no strength overlap, dosage form (tablet vs. lotion), and route of administration (oral vs. topical). These differences would decrease the potential risk of a medication error occurring between these two drug products.

Klorvess sounds similar to "Clobex". *Klorvess* contains potassium chloride and is indicated for the treatment of hypokalemia in various conditions as well as prevention of potassium depletion when dietary intake is inadequate in various conditions. *Klorvess* sounds similar to "Clobex" due to the similar pronunciation of "klo" and "clo". However, one may hear a difference between "klor" (pronounced "chl-or") and "clo" (pronounced "chloe"). The "vess" in *Klorvess* and "bex" in "Clobex" also sound similar. These two products differ in strengths (20 mEq vs. 0.05%), dosage form (tablet vs. lotion), route of administration (oral vs. topical), and directions of use (take # tablets per day vs. apply twice a day). However, a prescriber may give a prescription as "Klorvess, Use as directed, #30," which can be misinterpreted as "Clobex, Use as directed, 30 days supply or 30 mL (approximately 1 oz.)". According to the data provided by Thomson and Thomson. [redacted]. Also, according to Novartis, *Klorvess* has been discontinued since 2001. Since *Klorvess* is no longer on the U.S. market, the potential risk of medication errors occurring between these two drug products would be low.

Also, the establish name is not expressed in a consistent form among the package insert, carton labeling, and container labels. On the carton labeling and container labels, it lists the established name as "clobetasol topical lotion", and the package inserts states it as "clobetasol propionate" or "clobetasol propionate lotion". According to the USP, "topical lotion" is not listed as a dosage form; however, "topical solution" is listed. We recommend consulting Dan Boring (of the USAN council and LNC) for the proper designation of the established name.

III. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name "Clobex". This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

2. DDMAC finds the proprietary name, "Clobex", acceptable from a promotional perspective.

3. Provide final labels and labeling once available for review and comment.

4. We recommend consulting Dan Boring (of the USAN council and LNC) for the proper designation of the established name.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

/S/

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/S/

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennifer Fan
6/9/03 09:25:58 AM
PHARMACIST

Denise Toyer
6/9/03 10:05:39 AM
PHARMACIST

Carol Holquist
6/9/03 10:13:45 AM
PHARMACIST

Jerry Phillips
6/9/03 01:54:35 PM
DIRECTOR

NDA FILEABILITY CHECKLIST

NDA Number: 21-535 **Drug Name:** CLOBEX™ (clobetasol propionate) Lotion, 0.05%

Applicant: GALDERMA Laboratories, L.P.

IS THE CMC SECTION OF THIS APPLICATION FILEABLE? (Yes or No) _Yes___

Table 1 Fileability Checklist

The following parameters are necessary for initiating a full review, e.g. complete enough for review but may have deficiencies.

	PARAMETER	YES	NO	COMMENT
1	Is the NDA organized adequately for its CMC content?	X		
2	Are the CMC sections adequately indexed & paginated?	X		
3	Are the CMC sections legible?	X		
4	Are all facilities identified with full street addresses, contact names & CFN #s?	X		All sites were acceptable
5	Is there a statement that all facilities are prepared for GMP inspections?	X		All sites were acceptable
6	Has an environmental assessment or categorical exclusion been provided?	X		
7	Does the drug substance section contain controls?	X		
8	Does the drug product section contain controls?	X		
9	Has stability data been submitted to justify the requested expiry date?	X		
10	Has the applicant provided all requested data by the division during the IND & pre-NDA phases?			Most
11	Have draft container labels been provided?	X		
12	Has a draft package insert been provided?	X		
13	Has an Investigational Formulations section been included?	X		
14	Are there three Methods Validation documents?		X	Only 2 docs
15	Is a statistical consult required?		X	
16	Is there a separate microbiological section? Is a micro consult required?		X X	

EER REPORT ATTACHED

Table 2 STABILITY DATA REQUIRED FOR FILEABILITY

	STABILITY DATA REQUESTED	YES	NO
1	Does the NDA include 12 or more months of stability data?	X	
2	Does the stability data cover the expiry date?	X	
3	Does the stability data include **only** the largest & smallest container sizes?		X*
4	Does the stability data include all packages sizes?	X	
5	Are there tabular data for each size and batch?	X	
6	Are there graphical data for each size and batch?		
7	Is a statistical consult required?		X
8	Is a stability protocol included?	X	
9	Are the stability-indicating assays described?	X	
10	Is there the three-point stability commitment?	X	

* Stability data submitted includes all package sizes. See next item

Table 3 DMF INFORMATION

DMF #	DMF HOLDER	TYPE	LOA DATE	DATE OF LAST REVIEW
[redacted]		II	March 9, 2001	March 22, 2001
		II	July 5, 2001	Not reviewed*
		III	December 5, 2000	June 29, 2000**
		III	November 7, 2001	May 3, 2002
		III	May 31, 2001	March 20, 2001**
		III	August 3, 2001	August 3, 2000**

* Last update dated February 6, 2002

** Inadequate

Completion Date: November 13, 2002

Saleh A. Turujman, Ph.D.
Review Chemist

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader

Attachment

Cc: NDA 21-535
HFD-540/Division File
HFD-540/Chm/SATurujman
HFD-540/ChmTL/WHDeCamp
HFD-540/ProjMgr/MHarris
HFD-830/DivDir/CChen

C:\Data\My Documents\turujman\reviews\NDA\NDAs 2002\21-535 CLOBEX Lotion\NDA 21-535 FILEABILITY CHECKLIST.doc

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 21535/000	Action Goal:	
Stamp:	27-SEP-2002	District Goal:	28-MAY-2003
Regulatory Due:	27-JUL-2003	Brand Name:	CLOBEX (CLOBETASOL
Applicant:	GALDERMA LABS LP	Estab. Name:	PROPIONATE LOTION)
	14501 NORTH FREEWAY	Generic Name:	CLOBETASOL PROPIONATE
	FORT WORTH, TX 76177		0.5%
Priority:	S	Dosage Form:	(LOTION)
Org Code:	540	Strength:	0.5%

Application Comment:

FDA Contacts:	M. HARRIS	(HFD-540)	301-827-2020	, Project Manager
	S. TURUJMAN	(HFD-540)	301-827-2085	, Review Chemist
	W. DECAMP II	(HFD-540)	301-827-2041	, Team Leader

Overall Recommendation: ACCEPTABLE on 23-OCT-2002by J. D AMBROGIO(HFD-324)301-827-0062

Establishment: CFN 1628114 FEI 1628114
DPT LABORATORIES INC
307 EAST JOSEPHINE
SAN ANTONIO, TX 78215

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
Profile: LIQ OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-OCT-2002				TURUJMANS
SUBMITTED TO DO	08-OCT-2002	10D			DAMBROGIOJ
DO RECOMMENDATION	09-OCT-2002			ACCEPTABLE BASED ON FILE REVIEW	JFITCH
DALLAS DISTRICT RECOMMENDS APPROVAL OF THIS NDA ORIGINAL (21535/000) BASED ON THE 8/2001 PAI/GMP INSPECTION OF DPT LABORATORIES. THE INSPECTION WAS CLASSIFIED ACCEPTABLE.					
OC RECOMMENDATION	10-OCT-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: CFN [redacted] FEI 3002807208

DMF No: [redacted]
Responsibilities:

Profile: CSN OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-OCT-2002				TURUJMANS
OC RECOMMENDATION	08-OCT-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: CFN [redacted] FEI 3002808174

DMF No: [redacted] ADA:
Responsibilities:

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-OCT-2002				TURUJMANS
SUBMITTED TO DO	08-OCT-2002	GMP			DAMBROGIOJ
DO RECOMMENDATION	23-OCT-2002			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ
OC RECOMMENDATION	23-OCT-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Saleh Turujman
11/22/02 03:51:14 PM
CHEMIST

For your signature

Wilson H. DeCamp
11/22/02 03:55:50 PM
CHEMIST
concur

Division of Dermatologic and Dental Drug Products (HFD-540)

Pharmacology/Toxicology Checklist for NDA Filing Meeting

Date: 11/13/02
Reviewer: Paul C. Brown
NDA Number: 21-535
Sponsor: Galderma Laboratories
Product Name: Clobex Lotion
Drug Substance(s): Clobetasol propionate
Indication: corticosteroid-responsive dermatoses
Route of Administration: topical to the skin
Date CDER Received:9/27/02
User Fee Due Date (if filed): 7/23/03
Expected Date of Draft Review (if filed): 2/27/03

Note: This NDA was submitted under section 505(b)(2) of the FD&C Act. It refers to the Agency's finding of safety and effectiveness for the approved product Temovate E Emollient Cream. The sponsor has conducted an HPA axis suppression study comparing their product with Temovate E Emollient Cream. Therefore, much of the pharmacology and toxicology support for the current NDA is derived from reference to the NDA for Temovate E Emollient Cream.

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner that would allow a substantive review to be completed?
Yes

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review?
Yes

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed?
Yes

(4) Based upon a cursory review, does the presentation of data appear to be appropriate (consider tables, graphs, completeness of study reports, inclusion of individual animal data, appropriateness of data analysis, etc.)?
Yes

(5) Are all necessary nonclinical studies completed and submitted in this NDA?
Yes

(6) Please itemize the pivotal nonclinical studies included in the NDA and indicate any important nonclinical studies that were omitted.

Pivotal studies included:

A. **Single-dose rodent:** (from the literature)
Oral, subcutaneous and intraperitoneal in mouse and rat

B. **Single-dose non-rodent:** none

C. **Multiple-dose rodent:**
(from the literature):Three month and six month subcutaneous in rat, one month and three month topical in rat
(new studies): 13 week topical range finding study in hairless mice with and without simulated sunlight

D. **Multiple-dose non-rodent:** none

E. **Biodistribution and elimination:**
Liberation-penetration study *in vitro* with human skin

F. **Reproductive and Developmental toxicology:**
Preliminary study of embryo-fetal toxicity in rats, Main study of embryo-fetal toxicity in rats

G. **Special toxicology studies:** Local tolerance study in rabbits, Acute eye irritation in rabbits, Skin sensitization in guinea pigs

(7) Based upon a cursory review, do the pivotal nonclinical studies appear to have been adequately designed (e.g., appropriate numbers of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?
Yes

(8) As appropriate, were the test materials utilized in the pivotal nonclinical studies identical to the drug product or drug substance proposed for commercial use (including impurity profiles)? If not, or if this matter is unclear, please comment.
Formulations in published studies are unlikely to be identical to drug product. New studies appear to be conducted with the product proposed for commercial use.

(9) Based upon a cursory review, do the excipients appear to have been adequately qualified?
Polyoxyethylene glycol 300 isostearate (polyethylene glycol 300 isostearate, [redacted] is a noncompendial ingredient. It is not clear if this exact excipient has been used in other approved drug products. However, other very similar compounds have been used in approved drug products. It seems unlikely that the relatively minor differences between this compound and other members of this class of compounds would produce significantly different biological effects.

(10) Was the route of administration used in the nonclinical studies the same as the intended clinical route of administration?
Yes

(11) Has proposed draft labeling been submitted?
Yes

(12) From a pharmacology/toxicology perspective, should this NDA be filed? If not, or if you have additional concerns, please indicate your recommendations in the form of draft comments that may be transmitted to the sponsor.
Yes

/S/

Reviewing Pharmacologist Date Signed

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/s/

Paul Brown
11/26/02 02:31:42 PM
PHARMACOLOGIST

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application: (YES) NO

BIOPHARMACEUTICAL:

(1) On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin? ✓

(2) Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ✓

(3) On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin? ✓

(4) Are the Phase 1 studies of appropriate design and breadth of investigation to meet basic pharmacokinetic characterization requirements for approvability of this product? N/A

(5) If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceutics data to allow comparisons of and establish the equivalence of the product to be marketed and the product(s) used in the clinical development? N/A

(6) From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not? ✓

/S/

Reviewing ~~Medical Officer~~

/S/

Supervisory ~~Medical Officer~~

target date end of Mond

45 DAY MEETING CHECKLIST
NDA 21-535

FILEABILITY:

On initial overview of the NDA application:	YES	NO

CLINICAL:

1. On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X	
2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X	
3. On its face, is the clinical section of the NDA legible so that substantive review can begin?	X	
4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose- ranging studies)?	N/A	

This is a 505 (b)(2) application where the sponsor is using Temovate E Cream, 0.05% as the reference listed drug product. The frequency of application and duration is the same as Temovate E Cream.

5. On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Yes

Application Type: 505 (b) (2) (Y/N) Reference drug: Temovate E Cream, 0.05%

Identification of pivotal trials:

Pivotal Study #1: Protocol Number: CR.U9707.R02
Page Location in NDA: Protocol: Appendix 16.1, Vol. 30,, Page 3441 (page 177 of study report)
Study Report: Vol. 26, page 3264 (page 1 of study report)

Efficacy endpoints (Primary and secondary):
Primary

Success rate derived from the Global Severity Score at week 4 of treatment. Success is defined as a Global Severity Score of 0, 0.5 or 1. Clobetasol Propionate Lotion also has to be superior to its vehicle and non-inferior to Temovate® E Emollient Cream, 0.05% (RLD).

Secondary

Major secondary efficacy variables are erythema, plaque elevation, scaling, and pruritus.

How measured: Measured by severity scales.

Pivotal Study #2: Protocol Number: RD.06.SPR.18001
Location in NDA: Protocol: Appendix 16.1 page 180, Vol. 31; Study Report: Vol. 1.30 page 5159 (begins page 1 of study report)

Has the sponsor stated that this protocol is identical in design to Study #1? No

Is this an adequate multi-centered trial? Yes, 14 centers in the United States

Center	Patients Enrolled
2122	42
2029	28 (-1)
2128	23 (-5)
1170	21(-3)
429	18 (-1)
2067	18
2129	16 (-2)
2089	14 (-3)
2121	14 (-1)
2026	13 (-2)
2069	11 (-1)
2087, 2092, 2139	11 (-4)

Note: numbers in parentheses indicate discontinuations from study

Study Title: "The Safety and Efficacy of Clobetasol Propionate Lotion, 0.05% as Compared to its Vehicle and Temovate E Emollient Cream in the Treatment of Moderate to Severe Atopic Dermatitis: A randomized, Active- and Vehicle-Controlled, Investigator-masked, Parallel Comparison"

Study design: Randomized – yes; Double Blind -Investigator masked; Placebo controlled yes; Multicentered - yes

Indication: Same as for pivotal study #1

Study arms (dosage, duration, treatment length for each arm):

Three arms in the study: Clobetasol propionate lotion, Temovate E Emollient Cream, 0.05%, and lotion vehicle.
Dosage – application twice daily
Duration – two weeks

Efficacy endpoints (Primary and secondary):
Primary

Success rate derived from the Global Severity Score at week 2 of treatment. Success is defined as a Global Severity Score of 0, 0.5 or 1. Clobetasol Propionate Lotion also has to be superior to its vehicle and non-inferior to Temovate® E Emollient Cream, 0.05% (RLD).

Secondary

Global severity score (full-scaled), erythema, excoriation, induration/papulation, lichenification, oozing/crusting, dryness/scaling, and the Dermatologic Sum Score (DSS = the sum of the scores for erythema, excoriation, induration/papulation).

How measured: Asessed by severity scales.

	YES	NO
6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X	

Proposed indication from sponsor's draft labeling:

"Clobetasol Propionate Lotion, 0.05% is a super-high potent corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dematoses [redacted] Treatment should be limited to 2 consecutive weeks [redacted] total dosage should not exceed 50 g [redacted], per week [redacted]

Patients should be instructed to use Clobetasol Propionate Lotion, 0.05% for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS).

As designed, could endpoints in pivotal trial #1 support labeling?	X
As designed, could endpoints in pivotal trial #2 support labeling?	X

7. Are all data sets for pivotal efficacy studies complete for all indications (indications) requested? X

8. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? X

PreIND Mtg: Yes
IND number/s: 54, 230
PreIND Mtg Date: April 8, 1997
EP2 Meeting Date: September 20, 1999
Agency response to Phase 3 protocols: May 3, 2000
PreNDA meeting date: October 2, 2001

Do endpoints as described by sponsor in pivotal Study 1 conform to previous agency commitments? (Y/N/No previous commitment) X

Do endpoints as described by sponsor in pivotal Study 2 conform to previous agency commitments?(Y/N/No previous commitments) X

Are the pivotal trials multi-centered? Y/N X
Are there adequate numbers of patients enrolled? Y/N

9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?

The sponsor needs to provide separate line listings for cutaneous adverse events. The sponsor should also provide adverse events in a tabular form for all adverse events that occurred ≥ 1% and a separate listing in tabular form for cutaneous adverse events that occurred ≥ 1%. This should be done for each study and also combined in the integrated summary of safety.

10. Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population? X

11. Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? X

12. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? X

13. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?

The sponsor should provide any information regarding the marketing or pending applications of this product in other countries.

14. Has the applicant submitted draft -labeling consistent with 21CFR 201.56 and 21CFR 201.57, current divisional policies, and the design of the development package? X

15. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? X

16. Has the applicant complied with the requirements of the Pediatric Rule?

a) Is this an indication that would be applicable to the pediatric population? X
b) What pediatric ages are included in the protocol? Ages 12-17 years
c) Does the sponsor request pediatric labeling? What age groups?
d) What waivers, if any, are requested?

A waiver is not listed in the table of contents.

17. Financial disclosure of investigator

a) Does the NDA contain the appropriate form to comply with the filing requirement for Financial Disclosure for Investigators? X

18. From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. X

If certain claims are not fileable please state which claims they are and why they are not fileable.

Filing Review Issues

One filing review issue noted at this time is the fact that clobetasol propionate lotion, 0.05% appears to cause more HPA axis suppression than the reference listed drug product, Temovate E Cream, 0.05%. This may have an impact on the final recommendation for use of clobetasol propionate lotion, 0.05%.

/S/

Reviewing Medical Officer

/S/

Medical Team Leader

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/s/

Denise Cook
11/21/02 01:38:34 PM
MEDICAL OFFICER

Markham Luke
11/26/02 03:10:52 PM
MEDICAL OFFICER
Pediatric Waiver concern will not be conveyed at this time due to the enjoinment of the Pediatric Rule as per Project Management.

Statistical Review and Evaluation: Filing Meeting Review

NDA:	21,535/Corticosteroid
Submission Date:	9/25/2002
Name of Drug:	Clobetasol Propionate Lotion, 0.05%
Applicant:	Galderma Laboratories, L.P.
Indication(s):	Corticosteroid-responsive dermatoses
Rout of Administration:	Topically twice daily
Clinical Studies:	Two pivotal clinical trials (#9707 and 18001) and —supporting trials (#2651 and 2617)
Related INDs, NDAs:	IND ——
Clinical Reviewer:	Denise Cook, M.D., HFD-540
Statistical Reviewer:	Shiowjen Lee, Ph.D., HFD-725
Project Manager:	Melinda Harris, HFD-540

I. ORGANIZATION AND DATA PRESENTATION	YES	NO	N/A
***A. Is there a comprehensive table of contents with adequate indexing and pagination?**	_X_	___	___
@B. Are the original protocols, protocol amendments and proposed label provided?	_X_	___	___
*C. Are the following tables/listings provided in each study report?			
1. Patient profile listings by center (includes all enrolled patients).	_X_	___	___
2. Lost subject tables by center, which includes reason and time of loss.	_X_	___	___
3. Intermediate analysis summary tables (gender, age, race/ethnic, etc.).	_X_	___	___
@D. Is the data have been submitted electronically?	_X_	___	___
If the data have been submitted electronically, has adequate documentation of the data sets been provided?	_X_	___	___
If the data have been submitted electronically, can laboratory data be easily merged across studies and indications? **(No lab. data)**	___	___	_X_

II. STATISTICAL METHODOLOGY

		YES	NO	N/A
*A.	Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	_X_	___	___
*B.	For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)?	_X_	___	___
C.	Based on the summary analyses of each study, do you believe:			
*1.	The analyses are appropriate for the type data collected, the study design, and the study objectives (based on protocol and proposed label claims)?	_X_	___	___
*2.	Intent-to-treat (ITT and MITT) analyses are properly performed?	_X_	___	___
3.	Sufficient and appropriate references were included for novel statistical approaches?	_X_	___	___
*D.	If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?	___	___	_X_
*E.	Are there studies which are incomplete or ongoing?	___	_X_	___
*F.	Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline?	_X_	___	___

III. FILEABILITY CONCLUSIONS

From a statistical perspective, is this submission or indications therein, reviewable with only minor further input from the sponsor?

Yes, the submission is fileable from a statistical perspective. The randomization lists with dates of generation for studies 9707, 18001 and 2651 are requested to facilitate the statistical review.

/S/

Shiowjen Lee, Ph.D.
Mathematical Statistician, Biometrics III

/S/

Concur: Mohamed Alosh, Ph.D.
Team leader, Biometrics III

cc:
Archival: NDA 21,535
HFD-540/Div. File
HFD-540/Dr. Wilkin
HFD-540/Dr. Luke
HFD-540/Dr. Cook
HFD-540/Ms. Harris
HFD-710/Dr. Anello
HFD-725/Dr. Huque
HFD-725/Dr. Alosh
HFD-725/Dr. Lee
Chron.

This NDA filing review contains 3 pages.

* These items, if not included or if incorrect, are justifiable reasons for not filing the NDA.
@ These items, if not acceptable, are reason to consider not filing.
# It is the Agency's intent that all submissions be CANDARs or electronic in format in 1995. Clearly, we do not need CANDARs for every submission, but, just as clearly, we need data on disks if we are to do an expeditious review. Since the company, in all likelihood, used computers to do their evaluations, all data should be readily available to us on disk, at least, for our use in the review action.

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/s/

Showjien Lee
11/20/02 02:39:44 PM
BIOMETRICS

Mohamed Alosh
11/20/02 03:18:00 PM
BIOMETRICS

3 Page(s) Withheld

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-535	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug: Clobex (clobetasol propionate) Lotion, 0.05%		Applicant: Galderma Laboratories, L.P.	
RPM: Melinda Harris, M.S.		HFD-540	Phone # 301-827-2020
Application Type: ( ) 505(b)(1) (X) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): Temovate E, NDA 20-340	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	July 27, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II (X) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) (x) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	Yes
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	July 22, 2003
• Original applicant-proposed labeling	September 25, 2002
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC March 25, 2003 ODS tradename – June 9, 2003 ODS – May 5, 2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	September 25, 2002
• Reviews	yes
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	July 18, 2003, revised July 22, 2003
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	September 20, 1999
• Pre-NDA meeting (indicate date)	October 2, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	July 24, 2003
❖ Clinical review(s) *(indicate date for each review)*	July 24, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	May 7, 2003
❖ Biopharmaceutical review(s) *(indicate date for each review)*	August 1, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A/
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	June 27, 2003
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	June 27, 2003
• Review & FONSI *(indicate date of review)*	June 27, 2003
• Review & Environmental Impact Statement *(indicate date of each review)*	June 27, 2003
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: 10/23/02 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	March 20, 2003
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Galderma Laboratories, L.P.
14501 North Freeway
Fort Worth, TX 76177

RECEIVED
SEP 30 2002
MEGA/CDER

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 27 2002
CDR

2. TELEPHONE NUMBER *(Include Area Code)*

(817) 961-5000

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-535

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

3. PRODUCT NAME

Clobetasol Propionate Lotion, 0.05%

6. USER FEE I.D. NUMBER

4379

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See item 8, reverse side if answered YES)*

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Paul M Clark	VP Regulatory Affairs	25 Sept 02

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

USER FEE VALIDATION SHEET

NDA # 21-535 Supp. Type & # _____ UFID # 4379
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

2. (YES) NO APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.

3. YES (NO) SMALL BUSINESS EXEMPTION

4. YES (NO) WAIVER GRANTED

5. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. P (S) PRIORITY or STANDARD APPLICATION?

PM Signature / Date LST

LST
CPMS Concurrence Signature / Date

2/14/00

1 Page(s) Withheld

54 Draft Labeling Page(s) Withheld

E. ENVIRONMENTAL ASSESSMENT

The requested action for approval of the NDA application meets the requirements for categorical exclusion as stated in 21 CFR 25.31(b). The request exclusion is based on the calculations that were performed to show that the estimated concentration for the active pharmaceutical ingredient at the point of entry into the aquatic environment would be below 1 part per billion (ppb).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division Office):
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM:
Melinda Harris, M.S.
Project Manager
Division of Dermatologic and Dental Drug Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/18/02		21-535	New NDA	9/25/02

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Clobex (clobetasol propionate lotion) 0.05%		3S	ASAP if objections with the tradename PDUFA date 7/27/03

NAME OF FIRM: Galderma Laboratories, L.P.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER (SPECIFY BELOW): Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Please review the requested tradename "Clobex". The Division is requesting that the Sponsor reformat the Patient Package Insert into the Medication Guide Format. The bottle/box label, Physician package insert and patient package insert are attached. I will also send a hard copy.

PDUFA DATE: July 27, 2003
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC:
Archival NDA 21-535
HFD-540/Division File
HFD-540/RPM, Melinda Harris, M.S.
HFD-540/Reviewers and Team Leaders

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)	
Melinda J. Harris, M.S.	X☐ MAIL	☐ HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Melinda Harris
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office):
Division of Drug Risk Evaluation (DDRE)
HFD-430
PKLN 15B08

FROM:
Melinda Harris, M.S
Project Manager, HFD-540
Division of Dermatologic and Dental Drug Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 19, 2002		21-535	New NDA	September 25, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Clobex (Clobetasol Propionate Lotion) 0.05%		3S	Labeling Day scheduled for May 6, 2003

NAME OF FIRM: Galderma Laboratories, L.P.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:
  Labels(PPI, Carton/Container; PI) review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Labels for bottle/box, Physician Insert, and Patient Package Insert are attached. A hard copy will also be sent via courier. The Sponsor will be requested to reformat the PPI into the medication guide format.

Labeling Day has been scheduled for May 6, 2003. Please provide comments in a sufficient amount of time prior to the meeting.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Melinda J. Harris, M.S. Project Manager 7-2020	X☐ MAIL ☐ HAND
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Melinda Harris
11/19/02 03:28:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
Division of Drug Marketing, Advertising and Communications, HFD-42
PKLN Room 17B04

FROM:
Melinda Harris, M.S.
Project Manager, HFD-540
Division of Dermatologic and Dental Drug Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 20, 2002		21-535	New NDA	September 25, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Clobex (Clobetasol Propionate Lotion) 0.05%		3S	Labeling Day Scheduled on May 6, 2003

NAME OF FIRM: Galderma Laboratories, L.P.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
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- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ X OTHER *(SPECIFY BELOW)*:

New NDA labels

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
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- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Labels for the bottle/box, Physician Insert and Patient Package Insert are attached. A hard copy will also be sent via courier. The Sponsor will be requested to reformat the PPI into the medication guide format.

A Labeling Day has been scheduled for May 6, 2003. Please provide comments in a sufficient amount of time prior to the meeting.

'GNATURE OF REQUESTER elinda J. Harris, M.S.	METHOD OF DELIVERY (Check one) X☐ MAIL ☐ HAND
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Melinda Harris
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office):
[redacted]oy Blay, Ph.D.
Director, Regulatory
DSI, HFD-46
MPN1, Room 115

FROM:
Melinda Harris, M.S.
Project Manager
Division of Dermatologic and Dental Drug Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 10, 2003		21-535	New NDA submission	September 25, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Clobex (clobetasol proprionate) Lotion, 0.05%		3S	Labeling Day scheduled for May 6, 2003

NAME OF FIRM: Galderma Laboratories, L.P.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

Request for DSI audit

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
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- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

X☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Are the patients enrolled in the Ocala, Florida site (Dr. [redacted] acceptable for inclusion for efficacy evaluation for this NDA? The concern and reason for this request is that Dr. [redacted] is under criminal investigation by the FDA. There was no other investigator in the study and Dr. [redacted] according to the Sponsor, performed all the efficacy and safety evaluations.

SIGNATURE OF REQUESTER Melinda J. Harris, MS	METHOD OF DELIVERY (Check one) XO MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Melinda Harris
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